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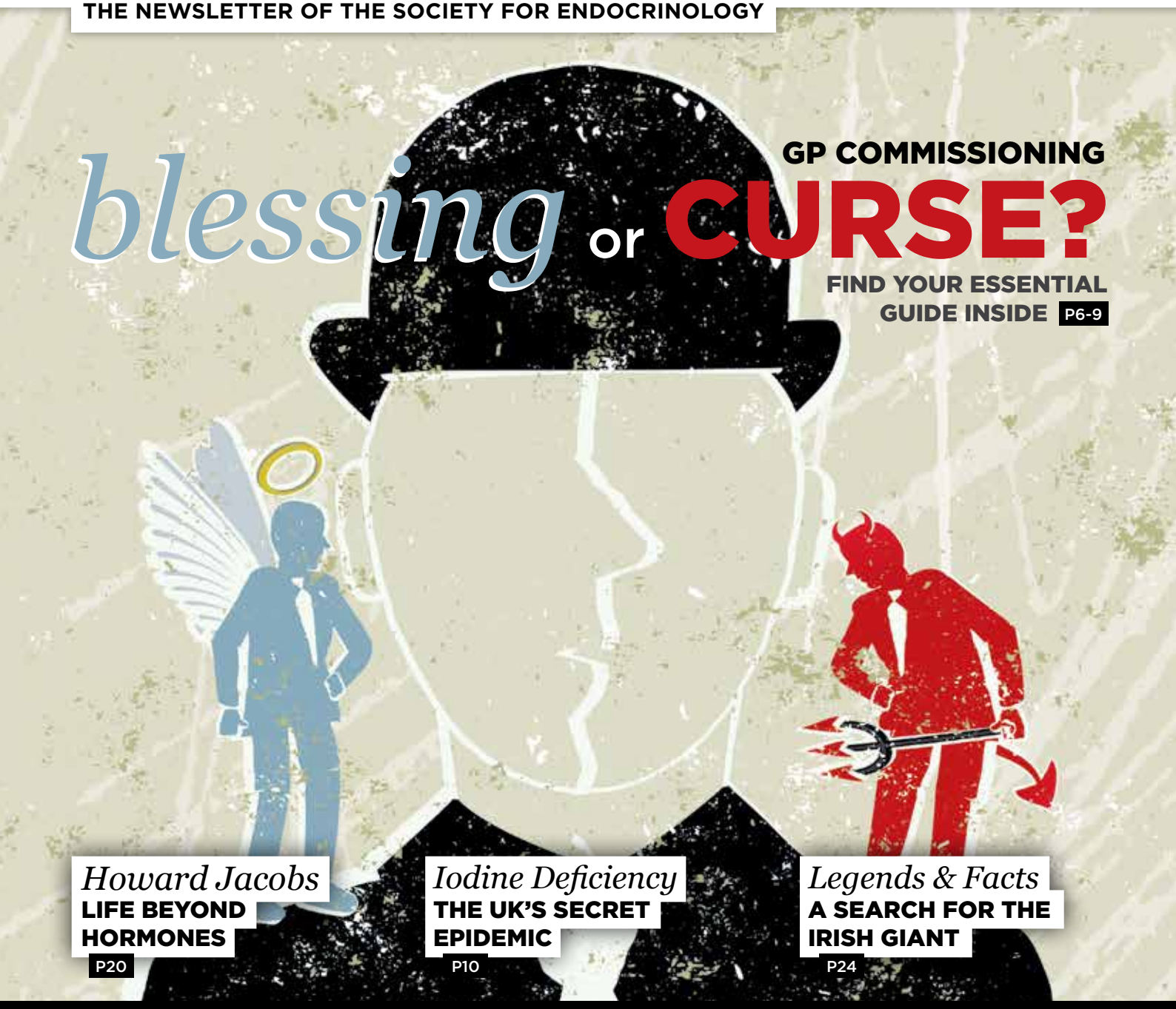
THE ENDOCRINOLOGIST

THE NEWSLETTER OF THE SOCIETY FOR ENDOCRINOLOGY



blessing or CURSE?

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A WORD FROM THE EDITOR...

So, this is the second issue since I took over the reins as Editor, and I hope you can see some green shoots of progress. We've actually had to keep some articles to one side this time, due to the high level of contributions, which is great. It is only a matter of time before publication in *The Endocrinologist* trumps a first author *Nature* paper!

It will be summer when you read this, but I am currently in a post-Society BES dust-settling situation. I always find it exceptionally hard to know where to put my conference paraphernalia (although I am finding my new pile of empty hessian Society for Endocrinology bags easier on the eye than the old blue ones). In truth, this Society BES was one of the best yet, and the usual moans from scientists about the number of clinical sessions (and vice versa) were strangely absent. Our new Editorial Board will keep us abreast of key scientific developments, and we will be providing an in-depth critical analysis of important endocrine papers, including high impact non-Society journals as well as our own publications.

The thorny subject of commissioning of endocrine services is covered in this issue. Most GPs tend to think that endocrinology is a dark art not to be meddled with, so we are probably safe. Nevertheless we need to make sure our patients get the opinions they deserve – ours!

The feature articles highlight the links between our subject and popular art and culture, underpinned by a raw fascination with the science of endocrinology. This combination of knowledge and enthusiasm for our specialty will outlive whatever transient political thoughts of the day preside, reinforcing that we as endocrinologists are here to stay.

As always, we are very grateful to all who have contributed this time round. We look forward to your help in continuing to raise the calibre of this magazine to stratospheric levels.

BEST WISHES
MILES LEVY

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Become a contributor...

Contact the Editorial office at **endocrinologist@endocrinology.org**

The Society welcomes news items, contributions, article suggestions and letters to the editor.
We would also like to hear your feedback on this issue of the newsletter.
Deadline for news items for the Autumn 2013 issue: 17 July 2013. Deadline for news items for the Winter 2013 issue: 16 September 2013.

CAREER DEVELOPMENT WORKSHOPS
STEVENTON, OXFORDSHIRE 18–20 OCTOBER

This new event is aimed at those registered for a PhD/MD or early career postdoctoral researchers with an interest in pursuing clinical academic or basic scientific research in endocrinology.

The Career Development Workshops will run along two distinct tracks (suitable for both basic scientists and clinician scientists):

- Career planning (aimed at mid- to late PhD delegates and early postdocs)
- Fellowship and grant application (aimed primarily at postdoc delegates)

Activities include:

- Critical appraisal of a journal article
- Learning presentation skills
- How to write a grant application
- Talks by representatives from grant-awarding bodies

Eight faculty members will be on hand to facilitate discussions, offer advice, and share experience.

Registration is free to members of the Society (subject to a £100 returnable deposit).

For more information see www.endocrinology.org/meetings/CDW

CLINICAL UPDATE 2013

Clinical Update 2013 takes place on 4–6 November in Bristol. It provides essential training for trainees and new consultants in endocrinology and diabetes, with a programme covering the national curriculum in endocrinology and diabetes issued by the Joint Royal Colleges of Physicians Training Board. The 3-day residential course comprises lectures and interactive workshops, to allow delegates to discuss best clinical practice in day-to-day scenarios. This year will see John Newell-Price take over from Wiebke Arlt as Programme Co-ordinator.

Wiebke Arlt and John Newell-Price

More information and online registration are available at www.endocrinology.org/meetings/clinicalupdate

HAPPY FIRST BIRTHDAY!

Endocrine Connections, the Society's new open access journal, is 1 year old this summer. The first year has been a great success, thanks to ongoing support from Society for Endocrinology Members and the wider endocrinology community. Submissions flow in steadily, with high quality papers published from across the breadth of the field.

Remember, we are still offering half price fees for the first 200 papers accepted. Find out more and view the latest content at www.endocrineconnections.com.

CONGRATULATIONS

We congratulate John Lazarus, who has been appointed the Regional Co-ordinator West and Central Europe for the International Council for Control of Iodine Deficiency Disorders. You can read more about his work on page 10.

NEW PRESIDENT-ELECT FOR ENDOCRINE SOCIETY

Richard Santen MD from the University of Virginia has been elected as President-Elect of The US Endocrine Society. Richard will start his term of office on 18 June 2013.

SOCIETY CALENDAR

16–17 September 2013
ENDOCRINE NURSE UPDATE
Stratford upon Avon

18–20 October 2013
CAREER DEVELOPMENT WORKSHOPS
Steventon, Oxfordshire

4–6 November 2013
CLINICAL UPDATE
Bristol

December 2013
REGIONAL CLINICAL CASES MEETING
Belfast

24–27 March 2014
SOCIETY FOR ENDOCRINOLOGY BES 2014
Liverpool

see **www.endocrinology.org/meetings** for full details

GRANT AND PRIZE DEADLINES

15 July
UNDERGRADUATE ACHIEVEMENT AWARD

15 August
CONFERENCE GRANT

27 November
EARLY CAREER GRANT

15 December
CONFERENCE GRANT

see **www.endocrinology.org/grants** for full details of all Society grants

ENDOCRINOLOGY, DIABETES & METABOLISM CASE REPORTS

This exciting new open access, online resource endorsed by the Society for Endocrinology will publish and link together case reports in endocrinology, diabetes and metabolism, facilitating discovery, connections and comparisons. Society Members will receive exclusive publication discounts. **Turn to page 16 for more details.**

HOT TOPICS

SOCIETY FOR ENDOCRINOLOGY OFFICIAL JOURNALS

Society members have free access to the current content of *Journal of Endocrinology*, *Journal of Molecular Endocrinology*, *Endocrine-Related Cancer* and *Clinical Endocrinology* via **www.bioscialliance.org.** *Endocrine Connections* is an open access journal and as such is free to all.

JOURNAL OF ENDOCRINOLOGY

TLR4 antagonist inhibits atherogenesis

Toll-like receptor 4 (TLR4) is an inflammatory mediator contributing to atherosclerosis and diabetes. Knockout mouse models have shown that inborn TLR4 deficiency reduces atherosclerosis, but whether treatments against TLR4 can induce similar effects on established atherosclerotic lesions was unknown.

Lu and colleagues addressed this question using treatment with TLR4 antagonist *Rhodobacter sphaeroides* lipopolysaccharide (Rs-LPS) in non-diabetic and diabetic *Apoe*–/– mice, where hypoglycaemia promotes vascular inflammation and accelerates atherosclerosis. Rs-LPS treatment over 10 weeks significantly reduced atherosclerotic lesion size in diabetic *Apoe*–/– mice in *en face* aortas and cross sections of aortic roots. Reduced levels of interleukin-6 and matrix metalloproteinase-9, and reduced monocyte/macrophage content in diabetic *Apoe*–/– atherosclerotic plaques, were also detected, indicating an anti-inflammatory response to TLR4 antagonism. Rs-LPS treatment was less effective in attenuating atherosclerosis in non-diabetic mice, but caused a reduction in serum cholesterol and triglyceride levels.

The results provide evidence for treatment of atherosclerosis by TLR4 inhibition, and further indication of a role for TLR4 in regulating lipoprotein metabolism.

Read the full article in *Journal of Endocrinology* **216** 62–71

JOURNAL OF MOLECULAR ENDOCRINOLOGY

Δ7/11, a prolactin binding protein

Prolactin is associated with cytokine functions in the immune system and mammary/prostate tumour incidence. Its binding proteins may be important in modulating its activity. Fleming and colleagues have shown that a secreted isoform of the receptor, Δ7/11, generated by alternative splicing of the transcript, can bind and potentially regulate the bioavailability of prolactin.

They used proximity ligation assays to detect the prolactin–Δ7/11 interaction. These assays are highly sensitive in detecting proteins and protein–protein interactions, resulting in efforts to develop them. For example, Hammond *et al.* 2012 (*PLoS ONE* **7**(7): e40405) combined them with microarrays to detect all pairwise interactions in a large group of target proteins. Such methods may be useful in research and diagnostic studies.

Δ7/11 was also shown to affect prolactin-stimulated cell behaviours. Its glycosylation directed Δ7/11 cellular localisation and secretion. Its significance *in vivo* is poorly defined, due to limited information on its source, despite its detection in serum and low incidence in breast tumour biopsies.

Read the full article in *Journal of Molecular Endocrinology* **50** 79–90

ENDOCRINE HIGHLIGHTS

A summary of papers from around the endocrine community that have got you talking.

Ptf1a-expressing cells in pancreas organogenesis

Islet cell transplantation and stem cell therapy have been investigated as a potential treatment for diabetes. The plasticity of the pancreas suggests that cellular transdifferentiation may also be a means to increase β-cell numbers in the injured pancreas.

Here, Wright and colleagues investigated the multipotency of Ptf1a-expressing multipotential progenitor cells during pancreas development and injury. Using an inducible lineage tracing method, Ptf1a cells were permanently labelled, allowing for the determination of Ptf1a progenitor potential at different developmental stages. Ptf1a cells are multipotent early in development, giving rise to acini, duct and endocrine cells, but switch to unipotent acinar progenitors later in pancreas development. Following pancreas injury, Ptf1a acinar cells were capable of transdifferentiation into ductal cells, a proportion of which could express the endocrine commitment factor Ngn3, leading to the expression of endocrine hormones and insulin.

The occurrence of these cells was rare, but if strategies that increase cell transdifferentiation could be found, the control of cell plasticity could add to the repertoire of treatments available for diabetes.

Read the full article in *Development* **140** 751–764

Efficacy and safety of dual RAS blockade

Dual blockade of the renin-angiotensin system (RAS) is extensively used to treat resistant forms of heart failure, hypertension, diabetic nephropathy, and proteinuria. Its efficacy and safety, however, remain controversial. This study by Makani and colleagues was a long awaited systematic review and meta-analysis of randomised controlled trials comparing dual blockade of the RAS with monotherapy, reporting data on either long term efficacy (≥1 year) or safety events (≥4 weeks), and with a sample size of at least 50.

This paper looks at all the available high quality evidence around the scenario that is common to clinical practice. Although dual blockade of the RAS may have seemingly beneficial effects on certain surrogate endpoints, it failed to reduce mortality and was associated with an excessive risk of adverse events such as hyperkalaemia, hypertension and renal failure compared with monotherapy. The risk to benefit ratio argues against the use of dual therapy.

Read the full article in *British Medical Journal* **346** f360

Blood-borne polypeptide influences circadian clocks in peripheral tissues

Disruption of circadian clocks has been associated with increased risk of disease. Here, Gerber and colleagues have investigated the mechanisms that co-ordinate the central clock, in the suprachiasmatic nuclei of the hypothalamus, and peripheral clocks that exist in many, if not all, tissues.

They have described the presence of a blood-borne factor that mediates circadian transcriptional cues in mouse liver tissue. The blood-borne factor is likely to be a polypeptide of 50–75kDa. Its presence was detected by unbiased screening of immediate early transcription factor activity in response to blood plasma (or sera) collected temporally through the day. This identified serum response factor (SRF) as a transcription factor that showed diurnal activity in response to staged blood plasma. Its activity was regulated by diurnal changes in actin dynamics, which facilitated rhythmical translocation of an SRF coactivator (MRTF-B) into the nucleus.

The authors suggest that a blood-borne factor mediates circadian regulation of tissue function through modulation of the Rho-actin-MRTF pathway resulting in rhythmical transcriptional activity of SRF and MRTF-B target genes.

Read the full article in *Cell* **152** 492–503

Hot Topics is written by Tony Coll, Karen Featherstone, Paul Foster, Paul Grant and Olympia Koulouri.

HT

ENDOCRINE-RELATED CANCER

Central neck dissection in thyroid cancer recurrence

Papillary thyroid cancer often features cervical lymph node metastases, which are a source of disease recurrence. Treatment generally involves thyroidectomy with central neck dissection, to remove metastatic lymph nodes. Substantial central neck dissection can lead to surgical complications, so optimising therapeutic benefit involves balancing this and potential disease recurrence.

In this study of 379 patients, Alzahrani and Xing assessed factors affecting the recurrence of papillary thyroid cancer after thyroidectomy. Patients that did not undergo central neck dissection had a low recurrence rate. Patients that underwent the procedure showed more aggressive tumour characteristics as the extent of central neck dissection was increased, and an increased rate of disease recurrence. A genetic mutation in the BRAF gene (commonly present in papillary thyroid cancer) was also associated with a high risk of papillary thyroid cancer and cervical lymph node metastases, suggesting the potential value of the BRAF mutation in the prediction of their presence.

Read the full article in *Endocrine-Related Cancer* **20** 13–22

ENDOCRINE CONNECTIONS

T3 beneficial in thyroid replacement therapy

Tri-iodothyronine (T3) and thyroxine (T4) are important in metabolism, bone growth, neuronal maturation and fetal development. T3, the main active hormone, is available within the cell following trafficking from the circulation or by conversion of T4 to T3 by intracellular deiodination.

Hypothyroid patients receive levothyroxine monotherapy to increase their T4 levels. However, recent guidelines indicate use of T3/T4 combination therapy in some situations. Faber and colleagues have compared the effects of T4 monotherapy and T3/T4 combination therapy on markers of T3 activity in peripheral tissues in 26 hypothyroid subjects in a double-blind, randomised, cross-over trial.

Levels of sex hormone-binding globulin (SHBG), N-terminal pro-brain natriuretic peptide (NT-proBNP) and pro-collagen-1-N-terminal peptide (PINP) (markers of liver, cardiac function and collagen production respectively) were determined. SHBG and PINP levels increased following combination therapy, whereas no change in NT-proBNP levels was detected.

These data indicate that peripheral tissues detected a difference in T3 bioavailability, potentially resulting from an altered T4/T3 ratio, and suggest that further research is warranted to assess the effects of T3/T4 combination therapy in hypothyroidism.

Read the full article in *Endocrine Connections* **2** 55–60

CLINICAL ENDOCRINOLOGY

Transition of CAH patients to adult care

Despite the need for life-long specialist input, only a small minority of patients with congenital adrenal hyperplasia (CAH) attend specialist adult services at any given time. The role of transition from paediatric to adult care is important in this regard, but this has not been systematically explored.

Gleeson *et al.* have found that a significant number of patients with CAH are lost to follow up during transition from paediatric to adult care. Introducing a Young Person Clinic did not appear to prevent loss of patients to follow up. Several factors, such as gender, severity of CAH phenotype, biochemical control and distance from tertiary services, played a role in successful transition. Patients who attended the first two appointments after transition were most likely to show ongoing engagement.

The study highlights the extent of poor disease control and lack of engagement with adult specialist services. It underlines the importance of adjusting services to meet the needs of young adults to achieve better long term outcomes.

Read the full article in *Clinical Endocrinology* **78** 23–28

Mechanism of melanocortin 4 receptor action

The pivotal role of the melanocortin 4 receptor (MC4R) in controlling energy homeostasis, and the fact that it is a cell surface-expressed G protein with known peptide ligands, have made it a potentially attractive pharmacological target. However, several 'off target' effects, including elevated blood pressure, have meant therapeutic progress with melanocortin agonist agents has been slow.

Patients with null mutations in MC4R develop obesity and hyperinsulinaemia but do not develop hypertension. To understand the role of MC4R on neurones in the brainstem and in the spinal cord, Sohn and colleagues used Cre-Lox technology to label and allow direct recording of specific neuronal cell types expressing MC4R. Thus they could provide a molecular and cellular mechanism for regulation of the autonomic nervous system by MC4Rs and link the observations to variations in insulin secretion and blood pressure.

Although by no means providing a solution to avoid off target effects, these data help parse metabolic function and molecular mechanism to very specific regions of the brain.

Read the full article in *Cell* **152** 612–619

Society for Endocrinology journals **now optimised for use on mobile devices!**

Causal relationship between obesity and vitamin D status

Obese patients have a higher risk of developing diabetes, cardiovascular disease and stroke, and have reduced life spans. Intriguingly, obesity is also associated with a higher risk of vitamin D deficiency, another increasingly common public health concern.

Due to confounding factors, it has been difficult to prove that obesity directly reduces circulating 25-hydroxyvitamin D (25(OH)D). Vimaleswaran and colleagues have used information from 42,024 participants from 21 studies, and showed that a 'BMI allele score', based on 12 BMI-related gene variants, was linked to both BMI and 25(OH)D concentrations. They found that a 10% increase in BMI led to a 4.2% decrease in plasma 25(OH)D. By also using a '25(OH)D allele score', based on 2 gene variants, they demonstrated this score was associated with 25(OH)D concentrations, but not BMI. This strongly suggests that obesity-related changes result in a reduction of available vitamin D.

Population-level interventions to reduce obesity should therefore also tackle vitamin D deficiency.

Read the full article in *PLOS Medicine* **10** e1001383

COMMISSIONING IN THE ENGLISH NHS: A BASIC GUIDE

WRITTEN BY EDMUND JESSOP

'Power, in the form of budgets, over local commissioning is to be given to Clinical Commissioning Groups of GPs, but specialised services are to be commissioned for the whole country by the NHS Commissioning Board.'

When a GP sees a patient, nine times out of ten, he or she does not refer the patient on. If that number slipped to eight times out of ten, hospital attendance would double, with catastrophic consequences all round. So what happens in hospitals is almost entirely determined by what goes on in primary care.

Two further truths. First, the GP is very well placed to know about the quality of treatment in his or her local hospital. Patients go there for treatment, and GPs see the results. But, secondly, GPs are not well placed to know what is going on in specialist hospitals far away. They may only send one or two patients a year to these specialist services, and can build no close relationship with the treating teams.

From all this, it follows that, if you wanted to control hospital costs and monitor quality, you would put as much power as possible in the hands of local GPs, but you would also want a separate system for specialised services.

And that is pretty much what the current reforms in England are about. Power, in the form of budgets, over local commissioning is to be given to Clinical Commissioning Groups (CCGs) of GPs, but specialised services are to be commissioned for the whole country by the NHS Commissioning Board.

LOCAL VS SPECIALISED

Commissioning is the planning, funding and monitoring of health services. A local diabetic service, for example, can be planned, funded and monitored by local GPs. There may be a need for another diabetic nurse, or perhaps a problem in the outpatient clinic which needs sorting out. A service for thyroid malignancy cannot sensibly be planned and monitored by the ten or more CCGs whose GPs will use a regional centre.

The precise distinction between local and specialised is set out in detail in a 300 page manual (http://bit.ly/16rbOxt). Most of endocrinology is included, but only a few diabetic services (such as pancreas transplant or services for patients with some very rare diabetic syndromes). Overall about 10% of the NHS spend is on the specialised services.

The Commissioning Board will have 27 Area Teams (i.e. about one for every 2 million of the population) to negotiate contracts and monitor performance for specialised services. The Board has also set up an advisory structure of 75 Clinical Reference Groups (CRGs) to give advice and steer policy on specialised services. There is a CRG for specialised endocrinology, and another for specialised diabetes. The CRGs agree the service specification and policies on high cost drugs. They will also agree suitable metrics for clinical monitoring, and generally act as a conduit for suggestions, ideas and ambitions from clinicians in the specialty.

SENATES ARRIVE, AS POLITICIANS DEPART

The simple logic of CCGs for 'local' and Commissioning Board for 'specialised' proved too brutal for some. In particular, hospital consultants felt they had been left out, with the result that no-one would have a properly rounded view of the NHS in any given locality. The remedy for this deficit was to introduce Senates, composed of GPs, consultants and other stakeholders, to give some kind of overview in each area.

Finally, ministers wanted to distance themselves from the day-to-day running of the NHS. Nye Bevan promised that the sound of a dropped bedpan in any NHS hospital would reverberate around Westminster, but the profession has long argued that management of the NHS should be taken out of the hands of interfering politicians. Politicians have agreed.

So the Act of Parliament gives control over the entire NHS in England to the Commissioning Board, and permits the minister only to write each year setting out a mandate for the next 12 months. No more visits by aggrieved patients to ministers' offices and lurches in policy. The hospital trusts, of course, already have their freedom from the Department of Health's chain of control: they are accountable only to regulators (albeit quite a lot of them) such as Monitor.

EDMUND JESSOP
Medical Adviser, National Specialised Commissioning Team

Dr Edmund Jessop qualified at Oxford and trained in public health. Since 2002, he has been medical adviser with the National Specialised Commissioning Team and its various predecessors.

SPECIALIST COMMISSIONING: A CLINICIAN'S PERSPECTIVE

WRITTEN BY TRISTAN RICHARDSON

THE JOURNEY OF SPECIALIST COMMISSIONING

The first whisper of 'specialist commissioning' for me was 3 years ago in Harrogate at the Society for Endocrinology BES meeting. Despite the late hour, there was a packed room in the depths of the conference centre with a captive audience, many of us hearing for the first time about what this was likely to mean.

The descriptions imparted elicited a variety of reactions from the audience, from a nonchalance and perceived smugness, to anger and concern over future job prospects and job satisfaction. Many came away with the attitude that this was never going to happen, and others thought that it was simply tertiary care 'feathering their nests' and solidifying their patient base and thus their futures. There was some understanding that this might benefit certain aspects of patient care but, to many of us at that time, that did not seem to be a driver for this change.

Was I one of those angry 'young' men? I suppose I was. Have I seen the light? Well, I'm happy to sit in a bright room and help steer specialist commissioning in the 'right' direction.

WHAT IS SPECIALIST COMMISSIONING?

Complex endocrinology requires a dedicated multi-professional team with experience in managing patients with multisystem needs, including medical, radiological, laboratory and surgical management support. Specialist commissioning aims to deliver high quality medical and surgical treatment for adults with agreed endocrine diseases, to promote their optimal future and quality of life.

The proposed commissioned services include:

- Specialist thyroid conditions (mainly thyroid malignancies)
- Calcium and bone conditions, such as complex 're-do' surgery for primary hyperparathyroidism and 'complex problems of calcium/phosphate handling'
- Pituitary/hypothalamic (excluding conditions such as microprolactinomas/incidentalomas etc)
- Adrenal conditions, such as congenital adrenal hyperplasia, adrenal Cushing's syndrome, Conn's and phaeochromocytoma
- Neuroendocrine tumour treatment, including carcinoid syndrome and insulinoma
- Familial endocrine conditions including multiple endocrine neoplasia
- Reproductive conditions, including intersexual states

Increased vigilance regarding clinical outcomes such as mortality, post-operative morbidity, remission and relapse rates will be accompanied by better monitoring of quality of life and improved participation in clinical trials.

The specialist services will be regionally located to ensure consistent national coverage. Not every centre will be expected or able to provide all specialist endocrine services, e.g. supra-regional medullary thyroid cancer centres.

WHY IS IT HAPPENING?

One of the many differences between diabetes and endocrinology is the evidence base for conditions seen within either speciality. Specialist commissioning will aim to deliver best practice in rare disorders where limited evidence exists through multi-professional management strategies. Appropriate shared-care arrangements using standardised protocols between local and national services, with care delivered as close to patients' homes as much as possible, will be expected. Not all centres will have all the expertise required to deliver all specialist endocrinology services, but there will be active communication between regional hospitals to facilitate acute and follow-up patient care.

WHAT ARE THE ISSUES?

One of the difficulties with commissioning services is that practice varies throughout the land. We understand how our local GPs differ. There is also, of course, variation within secondary and tertiary care.

One of the concerns of secondary care was being tarnished with a brush of perceived mediocrity. At a time when our secondary care colleagues are under immense pressure to move much of their diabetes practice to primary care (and community diabetes), up comes specialist commissioning and threatens to take away their 'endocrinology'. A future of unending post-take ward rounds and elderly 'struldbrugs' was beckoning. Paranoia and depression could easily have set in – if only we had had time to sit and actually consider this in 2010.

However, here it is, and I don't think many of us would argue with the sentiments that are now in the public domain. Specialist care in the appropriate specialist centre for appropriate patients is appropriate. This doesn't mean secondary or tertiary, but simply care where the expertise is. Indeed, many of us would be keen to pass on those complex patients in the knowledge that they were in 'safe' hands, whilst many of us in secondary care would also feel happy to be assessed by the proper body to verify our level of expertise.

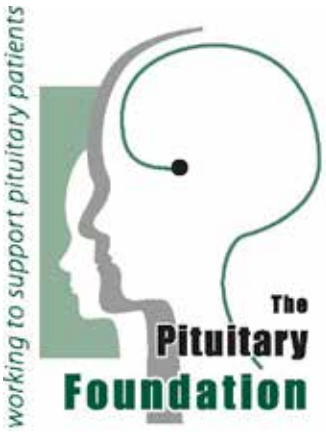
There will be teething problems: local differences in practice, patient preferences, lack of understanding by Clinical Commissioning Groups, communication issues between centres, loss of local expertise, worries over whether centres hand patients back ... the list goes on. If the process of delivering commissioning does not carefully involve open communication between all parties (and there is much work to be done), local centres will be at risk of losing valuable specialist expertise, patients will have diagnoses missed, or perhaps over-diagnosis may occur, threatening valuable NHS resources. However, let's not forget the potential benefits of specialist, high quality, world-class services as the end game.

There is much to do, but the ball has started to roll. Frailties are less than they were and the potential benefits to patients are perhaps more apparent. Sitting in a bright room, I feel more confident about the process, aims and outcomes. All concerned need to continue to be expansive in seeking opinion and inclusivity, in order for a smooth transition into specialist commissioning.

TRISTAN RICHARDSON
Clinical Review Group for Specialist Endocrinology Commissioning

Dr Tristan Richardson is Consultant Endocrinologist at Royal Bournemouth Hospital, a Fellow at Bournemouth University, and Western Comprehensive Local Research Network Lead for Endocrinology. He sits on the Society's Public Engagement and Clinical Committees and is a member of the Clinical Review Group for Specialist Commissioning for Endocrinology.

THE ADULT SPECIALISED ENDOCRINOLOGY CRG: THE PATIENT REPRESENTATIVES' PERSPECTIVE



WRITTEN BY PATSY PERRIN, PAT MCBRIDE & SARAH BAKER

At times, we have felt like Alice in Wonderland coping with all the NHS commissioning jargon, but common sense won through, with the help of our Clinical Reference Group (CRG) Chairman John Wass and our NHS Commissioning Manager Matthew Johnson. The key issues we raised have been heard and incorporated into the specification.

Our main task is to represent all patients with endocrine disease, during the process of helping to set out the service specification. This means considering not only a wide range of endocrine conditions, some of which are very complex, but also the overall patient experience, especially as many endocrine conditions are lifelong and heavily reliant on day-to-day self management.

We believe that, to do this well, it requires thinking beyond the specialist clinic, and into other domains where the patient may be particularly vulnerable and the knowledge of rare endocrine conditions appears to be much lower. It also means grounding that perspective in an everyday reality in which the boundaries between primary, secondary and tertiary care are truly facilitative, and sufficiently flexible, so that patients can be seen in the appropriate setting at any time, to achieve the best possible outcome for the individual patient. Good channels of communication, up and down the line, are essential.

Broadly speaking, the key areas of importance are:

EARLY DIAGNOSIS AND REFERRAL

It is vital that endocrine conditions are recognised sooner rather than later at GP level, with fast track referral to an endocrinologist competent in that particular condition. Raising awareness amongst GPs, secondary care services and others is a critical component here. Bearing in mind the often disparate, non-specific symptoms of many endocrine conditions, this is not an easy task, but one of which we must not lose sight.

ADEQUATE PATIENT INFORMATION

It is very important to ensure the patient has sufficient, comprehensive information and support at all stages. The patient experience seems to vary in this regard. We view patient education/health literacy as being very important to recovery and living with your condition, in particular being made aware of patient support groups. In some cases, patients, paramedics and all medical teams, regardless of specialty, need to be aware of potential life-threatening complications and how to prevent and manage them. Endocrine emergencies occur in non-endocrine clinic settings: at home, in public places, at the GP surgery or when being 'blue-lighted' to A&E. This is particularly important for patients taking hydrocortisone and, to this end, a national red flag protocol has been specified, with provision for refresher emergency injection sessions as a standard component of the annual review.

HIGH QUALITY SPECIALIST TREATMENT WITH CONTINUITY OF CARE

Specialist treatment, quality and continuity of care – well, these are what the CRG recommendations are all about! As part of this, we have advocated and endorsed the following: clear clinical pathways; the provision of specialist endocrine care which may be lifelong; listening to the individual patient's needs and preferences; vigilant monitoring for, and careful management of, co-morbidity; recognition and understanding of ordinary, daily difficulties that can undermine good self-management. The service specification now calls for a minimum 56-day script for lifelong medication, for example. In some cases, this would double the length of prescription that is currently regionally authorised.

The drafting of the service specification has been both challenging and worthwhile. As it is also an iterative process, we hope to continue to contribute to its content.

PATSY PERRIN, PAT MCBRIDE & SARAH BAKER

Sarah Baker is a Research Assistant/Teaching Associate at Oxford Brookes University.

Pat McBride is The Pituitary Foundation's Patient Support Manager.

Pasty Perrin is a former trustee of The Pituitary Foundation and was a patient representative for the NICE appraisal of growth hormone.

TELL US YOUR VIEWS...

We're keen to hear your thoughts and perspectives on the current changes to the NHS. What are your experiences on working with Clinical Commissioning Groups and specialist commissioning? What implications do you think these changes will mean for endocrinology?

Send us your thoughts to **endocrinologist@endocrinology.org**

LIFE IN THE 'BRAVE NEW WORLD'

WRITTEN BY TONY COLL

Given that you are reading this, the world probably didn't stop turning this April. The behemoth that is the Health and Social Care Act will have lumbered into action, aiming to improve services in the face of increasing demand and cost, all the while shackled by the unenviable state of the public finances.

The most obvious change will have been the flurry of name changes and games of musical chairs that plague reorganisations. The work of SHAs will be taken on by LETBs and HEE. PCTs will have gone, replaced by CCGs, trained by CSUs and supported by the NHSCB.* Good news for stationers, website designers and signwriters. Hopefully, by now, everyone will be sitting at the right desk, writing documents with the correct masthead and answering emails with an approved footer and disclaimer.

So how to respond to such upheaval? The 'newspeak' muddle of the ever-changing titles can be hugely disheartening. In response to the grand building project forced upon the weary animals on the farm, Orwell's donkey anti-hero Benjamin merely commented, 'Windmill or no windmill ... life would go on as it had always gone on – that is, badly.'

'Consider for a moment the excellent work that you and your fellow endocrinologists are already doing.'

Pessimism as a self preservation strategy is understandable, yet it brings about little promise of making progress out of change, and the potential scope of what is currently underway is big and not going away. Negativity can also rapidly slide into self-denigration and lead to problems in a discipline that make it ripe for 'reconfiguration'. But hang on in there. Let us not start tearing strips off each other just yet. Rather consider for a moment the excellent work that you and your fellow endocrinologists are already doing.

DIAGNOSIS

You expend a lot of effort on making the correct diagnosis and, whenever possible, seek aetiology to deal correctly with the presenting symptoms and signs. You know that this is not because you like arguing over how many angels could dance on the head of a pin, but because you know it matters. Recall those patients you'll have heard of, who underwent surgery at the wrong end of the pituitary-adrenal or pituitary-gonad axis. Talk to the patient with the insulinoma who skidded around from crisis to crisis until someone eventually took them seriously and considered that those funny turns weren't really normal after all. Ask someone with HNF1A–MODY (maturity onset diabetes of the young) if they wish to forego their sulphonylurea and return to insulin.

PATIENT FIRST

You believe disease classification and treatment should be based on pathological process, not on a patient's current geographical location on the planet. You are rightly proud of the multidisciplinary team you are a part of, not because of the bricks and mortar they occupy but because of the skills and dedication they continue to show, and the essential services they provide in a way that simply doesn't exist anywhere else in the health economy.

You are very good at managing people out of crises and getting much better at helping patients ameliorate the complications of condition and treatment. You try hard all the time to keep up to date with the ever increasing but very welcome developments in your field. You realise that achieving total cure can be difficult, but are well used to playing the long game and supporting people to remain active and independent. You lobby hard to make sure your patients can get access to new devices, treatments and educational programmes that can empower them to remain well and in control of their disease throughout their life. You take no joy whatsoever in seeing them admitted through the front door of the hospital in a metabolically parlous state.

You are glad that you have been trained in rational, integrative physiology so you can bring clarity and rigour to the tricky clinical problems presenting in your patients. This includes patients you see whose disease burden originates from pancreatic dysfunction.

THE MARCH OF PROGRESS

And when you read the statement contained in the bumf that is being circulated in support of the new Act that says 'it is our intention to create a culture of innovation and research that is embedded at every level in both the NHS and public health[1]' you think it is time to put up bunting and send in the marching bands. Hurrah – interventions based upon rational thought and mechanistic understanding!

So, a brave new world? Not really; are improving quality of care, reducing inequalities (in a positive direction), managing care for people with long term conditions, innovating and supporting collaboration so novel to you? Your biggest worry is that it seems no-one had understood what you were already doing and how you continue to strive to do better. Now who do I write to about that again?

TONY COLL

Dr Tony Coll is a University Lecturer at the University of Cambridge and Honorary Consultant Physician at Addenbrooke's Hospital, Cambridge. He is also Associate Editor of The Endocrinologist.

REFERENCE

1. Department of Health 2012 Factsheet C8: Embedding research as a core function of the health service – *the Health and Social Care Act 2012*. http://bit.ly/X8ItFl

*A note for those whose 'acronym training' is not yet complete: The work of **strategic health authorities** will be taken on by **local education and training boards** and **Health Education England. Primary care trusts** will have gone, replaced by **clinical commissioning groups**, trained by **commissioning support units** and supported by the **NHS Commissioning Board.**

IODINE DEFICIENCY: STILL A WORLDWIDE PROBLEM

WRITTEN BY JOHN LAZARUS

‘The UK lies between Angola and Mozambique in the top 10 iodine-deficient countries in the world.’

Iodine deficiency (ID) still affects up to 2 billion people worldwide, including 285 million school-age children. The condition has effects on growth and development and is the commonest cause of preventable mental deficiency worldwide. While significant improvements in the consumption of iodised salt have been made in many countries in the past 25 years, up to 50% of children in Europe live in an iodine-deficient environment.

The International Council for Control of Iodine Deficiency Disorders (ICCIDD, www.iccidd.org) was founded in 1985. It recognised a spectrum of ID disorders ranging from cretinism in severe deficiency (IQ <40: urinary iodine <20µg/l) to a 5 point loss of IQ in areas of mild to moderate deficiency, despite normal maternal thyroid function during gestation.

During the past century, the prevalence of goitre due to ID has reduced significantly in many European countries so that this condition is now rare. In the UK, this was not due to any legislation concerning the supply of iodine to the population, but occurred in a laissez faire episode, during which milk was consumed in increasing quantities and cattle cake containing iodine was administered to cows, particularly in wintertime. Milk consumption has declined over the past two decades, and a national survey measuring urinary iodine in 13-year-old schoolgirls from nine UK centres identified mild to moderate ID in two-thirds of the sample population. This is important in schoolgirls because they will become pregnant in years to come, and adequate maternal thyroid hormone is critical for normal fetal brain and nervous system maturation.

Randomised controlled trials of iodine supplementation in pregnant women in Spain with mild ID have shown that children whose mothers received iodine perform better in IQ tests than those whose mothers did not. Randomised trials of iodine administration to 9-year-old schoolchildren in several countries document improvements in cognitive ability in children receiving iodine compared with carefully matched control children.

In a UK study by Bath *et al*. (*Lancet* 2013 in press), 8-9-year-old children of mothers followed in the ALSPAC (Avon Longitudinal Study of Parents and Children) cohort showed impaired cognitive performance related to maternal urinary iodine in pregnancy.

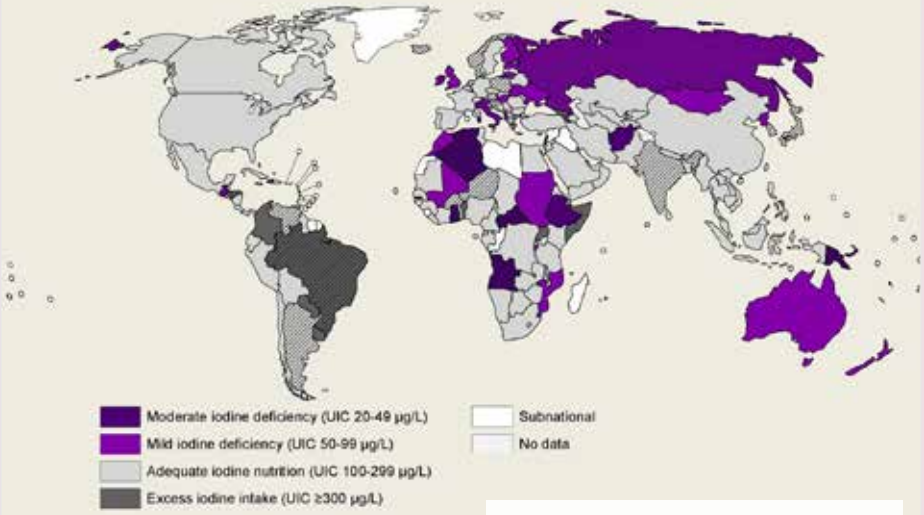
In fact, the UK lies between Angola and Mozambique in the top 10 iodine-deficient countries in the world relating to the number of schoolchildren at risk. There has been no UK legislation regarding the use of iodised salt either for household consumption or for use in processed food manufacturing. A survey of salt samples purchased from five supermarkets in the UK showed only 5% with adequate iodine content. In the opinion of the UK Iodine Status Strategy Group (UKISS), there is a requirement to pursue appropriate advocacy relating to the UK iodine situation, so that the Government and public health authorities can institute preventive action. The UK should not be an underdeveloped country in this context. The ICCIDD must strive to correct ID in all European countries.

JOHN H LAZARUS

Professor John Lazarus is from Cardiff University. He is Regional Co-ordinator, West & Central Europe International Council for Control of Iodine Deficiency Disorders and Chair of the United Kingdom Iodine Status Strategy Group.

More information can be found at: www.iccidd.org.

2012 National iodine status based on median (UIC) in school-age children.



UIC = Urinary Iodine Concentration

FURTHER READING

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Vanderpump MPJ *et al*. 2011 *Lancet* **377** 2007–2012.

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VOICE OF THE FUTURE

Part of National Science and Engineering Week 2013, the 'Voice of the Future' event on 20 March provided a platform for young scientists, at various stages of their careers, to press renowned figures on matters concerning the scientific community at large.

Four of the Society for Endocrinology's Young Endocrinologist Members had the opportunity to attend this event, organised by the Society of Biology and supported by their funding group for parliamentary affairs.

Within the walls of Portcullis House, London, these young scientists who, in years to come, will be at the forefront of their own respective fields, questioned the Government Chief Scientific Adviser, Sir John Beddington, the Minister for Universities and Science, Rt Hon David Willetts MP, and Shadow Minister for Higher Education and Science, Shabana Mahmood MP on topical issues. Ranging from women in science to stem cells, no stone was left unturned when it came to testing the speakers on matters central to scientific disciplines.

As the session drew to its end, it was clear the event would have a lasting effect. It had been an opportunity to gain an appreciation of how Parliament and Government determine various scientific policies, and to realise that such decisions are no easy task. It is not simply a matter of blindly pursuing the 'hottest' new trends in science but of ensuring that the policies implemented are acceptable to the community at large, by scientists and non-scientists alike.

You can watch the full proceedings at http://bit.ly/10c45iX.

MUHAMMAD KHAN
4th year medical student, University of Liverpool

Society representatives at Voice of the Future

WITH REGRET

We are sorry to hear of the recent deaths of Senior Members, Professor J Strong, Edinburgh, Dr WF Coulson, London, and Professor R Edwards, Cambridge. A further tribute to Professor Edwards will follow in the next edition.

CONGRATULATIONS

We are pleased to announce that Society Member Phillip J Monaghan (Christie Hospital, Manchester) has received the '2012 Specialty Research Medal Award in Clinical Biochemistry' from the Royal College of Pathologists for his paper 'Comparison of serum cortisol measurement by immunoassay and liquid chromatography-tandem mass spectrometry in patients receiving the 11β-hydroxylase inhibitor metyrapone' (*Annals of Clinical Biochemistry* 2011 **48** 441–446).

CARVING OUT A NICHE – THE ROLE OF THE CAREER DEVELOPMENT WORKSHOPS

FROM OUR SCIENCE COMMITTEE CORRESPONDENT

The first time I went to a Science Committee meeting I got distracted and ended up lost in the wrong building. I was lured in by the Art Deco honeytrap that is home to the Royal Institute of British Architects, a carved temple to talent and creativity for future generations to admire.

We meet a few doors along at the Institute of Physics. This converted Georgian townhouse was once home to John Buchan, a polymath who was brilliant at everything he tried (classics scholar, lawyer, merchant banker, publisher, war correspondent, Governor General of Canada, plus the odd classic spy thriller).

Our discussions happen in the Phillips room, named after one Major Charles Edmund Stanley Phillips. Born into wealth and educated at home, he was the quintessential 'gentleman scientist'. Working out of his self-crafted domestic laboratory, he was a leader in developing the scientific basis of radiotherapy and establishing medical physics in this country.

Also an accomplished musician and painter, he was not averse to combining artistic and scientific creativity. Phillips incorporated the thermochromic compound mercuric iodide into one of his paintings. By installing a heater behind it, he could amaze his friends with the evolving yellows and oranges in the sky as the colours changed with the temperature.

Few of us develop the CV of Buchan or enjoy the enviable financial independence and creative genius of Phillips. Yet the desire to do something that one is good at and enjoys is more universal. Even when that niche is found, there is the continuing need to feel that your work is important and will have some impact beyond the day to day.

If you are lucky, your ascendency will be signposted and straightforward, but it is easy to be led astray. Journeys can of course sometimes be the best part of the trip, but there is much to commend a clear steer and the sage advice of people who have been and done what one wishes to become.

We are therefore delighted to introduce the Society's Career Development Workshops, starting on 18–20 October in Steventon in Oxfordshire. To focus on the needs of different stages of career development, two tracks will run concomitantly: a 'career planning' stage for PhD and early postdoctoral fellows, and a 'fellowship/grant application' stage for more experienced postdocs looking to leap into independence.

Working on your CV and fellowship applications will be an integral part of the weekend's activities. This will be relevant to both basic and clinical researchers and we're aiming for no more than 30 people. For more information, see www.endocrinology.org/meetings/CDW and the details on page 3.

TONY COLL

Send your views to our science correspondent endocrinologist@endocrinology.org

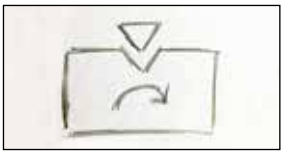
MOVING WITH THE NEW ERA...

By now you will have started to see some key elements of the Society's new identity coming through in our communications, such as a new look *The Endocrinologist*, the Annual Report, and the Society website.

The Society's new image represents how we as a Society view ourselves, and how we want to be viewed by other stakeholders and the general public alike. It also represents our values (Engage, Support, Advance), the core principles which underpin all that we do.

OUR LOGO INSPIRATION

What you may not know is that our logo inspiration came from a Society Member, Saffron Whitehead. During one of the early research workshops held by a neutral facilitator, Members were asked to draw what they felt best represented endocrinology. Saffron captured something which was simple yet understandable by those linked with endocrinology.



Saffron's original drawing

Society for Endocrinology

Our new logo

A logo needs to be instantly recognisable, aesthetically pleasing, and one that Members can relate to and associate with. Taking the simple form as a starting point, our creative team produced the new Society for Endocrinology logo – the central 'dot' within the multi-coloured curve represents a hormone binding with a receptor.

NEXT STEPS

This 'change for good' programme is about much more than just an image/logo changing, so to find out more about what is happening next in the Society visit www.endocrinology.org/new-era. The future holds some very exciting times for endocrinology, the Society and you, our Members... Watch this space.

FEEDBACK

Thanks to all of you who have sent us some fantastic feedback about the current changes taking place, including this quote from a Member:

'Love the new look journals and it was about time the old E was modernised!'

Please do keep the comments coming in. Let us know what you think of the changes, visit www.endocrinology.org/new-era to submit your feedback, or email endocrinologist@endocrinology.org.

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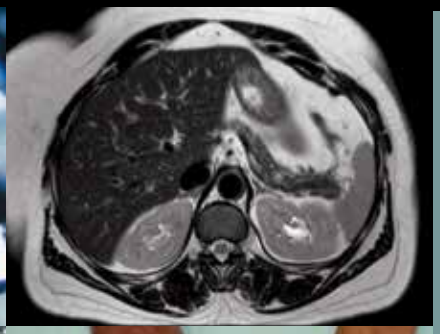

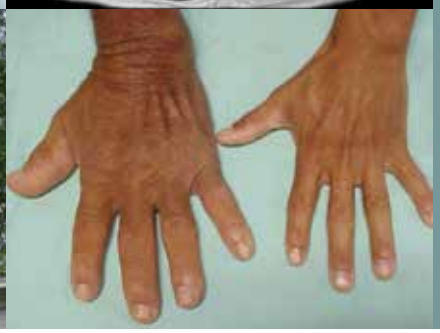

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YOUNG ENDOCRINOLOGISTS' CLINICAL PRIZE LECTURE 2013: Evaluating *Men1* gene replacement therapy for MEN1-associated NETs

WRITTEN BY GERARD WALLS

Gerard Walls is this year's Young Endocrinologists' Clinical Prize Lecturer. Here, he summarises his studies on neuroendocrine tumours (NETs) in multiple endocrine neoplasia type 1 (Men1).

I focused my studies on two conundrums in the MEN1 syndrome. First, why tumours develop in only some endocrine tissues, whilst the *Men1* mutation is expressed in all cells. Secondly, why there is a predominance of prolactinomas and gastrinomas, as opposed to other tumours in the pituitary and pancreas respectively.

Examining these questions in man is problematic because of the difficulty of obtaining tumour specimens at several different stages and time-points, and so I became involved in the development of a knockout mouse model for MEN1. These *Men1*+/– knockout mice develop parathyroid, pancreatic, pituitary and adrenal tumours, associated with an increased mortality of 30%. Thus, the *Men1*+/– mice are representative of MEN1, and I used this model to answer the following questions:

- whether intrinsic proliferation rates contribute to the cell types that develop MEN1-associated tumours
- whether restoration of a normal copy of the *Men1* gene may be used as a treatment for MEN1-associated NETs.

To assess *in vivo* proliferation rates, I used 5-bromo-2-deoxyuridine (BrdU), a thymidine analogue, that is incorporated into newly synthesised DNA during the S-phase of the cell cycle. BrdU was administered continuously in drinking water to *Men1*+/– mice for 1, 4, 8 or 12 weeks. Immunohistochemistry revealed that NETs had increased proliferation of less than 2% per day compared with under 0.1% in normal tissues. Time-course analysis of BrdU incorporation over 12 weeks demonstrated that pancreatic, pituitary and adrenal NETs had second-order growth kinetics, with a proliferating compartment of 20–40%, and that wild type tissues had first-order kinetics.

Furthermore, mathematical modelling of NET growth demonstrated that among pancreatic NETs, insulinomas would develop by 12 months of age, but somatostatinomas, PPomas, and glucagonomas would develop at about 30 months, which is beyond the normal lifespan of mice. Similarly, pituitary prolactinomas and somatotrophinomas developed by 15 and 18 months of age respectively, but corticotrophinomas required around 30 months to develop. Thus, mathematical modelling of proliferation rates suggested that intrinsic proliferative properties of endocrine cell types contributed to the frequent occurrence of insulinomas and prolactinomas in MEN1.

An important advance for the treatment of tumour suppressors, such as MEN1, would be gene replacement therapy. So we generated a replication-deficient adenoviral vector, containing the normal *Men1* gene, for direct injection into NETs. We chose the pituitary NETs, as opposed to pancreatic NETs, as they usually occur as a single tumour mass (as opposed to multiple tumours in the pancreas), are well localised, and are accessible to direct injection.

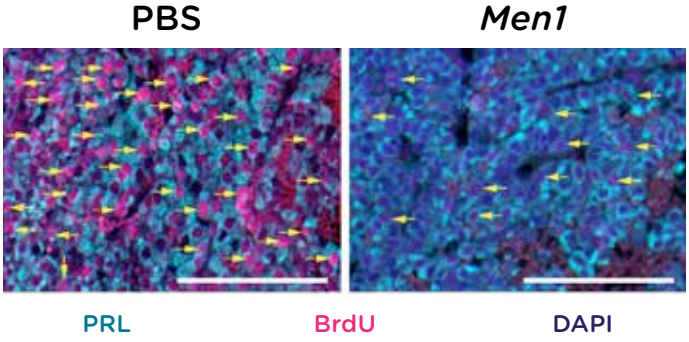
Our studies demonstrated expression of menin 4 weeks after a single vector injection, and that NET proliferation was reduced by up to sixfold, compared with controls, without significant adverse effects or increased mortality. Thus, proof of concept for *in vivo Men1* gene replacement therapy for inhibiting NET growth in MEN1 was established. The development of *Men1* gene therapy is likely to be of use in MEN1 patients for the treatment of anterior pituitary, pancreatic and thymic NETs, and also in equivalent NETs of non-MEN1 patients, as more than 40% of these have *Men1* mutations and loss of menin expression.

GERARD WALLS

Dr Gerard Walls is an Academic Clinical Lecturer in General Surgery at the Academic Endocrine Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Department of Medicine and Nuffield Department of Surgical Sciences at the University of Oxford.

FURTHER READING

- Walls GV *et al.* 2012 *Cancer Research* **72** 5060–5068.
- Walls GV *et al.* 2012 *Endocrinology* **153** 5167–5179.
- Walls GV *et al.* 2013 *Endocrine Abstracts* **31** YEP1.1.



Pituitary tumours were injected with either saline (PBS) or *Men1* gene therapy vector (*Men1*). Proliferating lactotrophs were labelled for prolactin (PRL, turquoise) and 5-bromo-2-deoxyuridine (BrdU, pink). Fewer BrdU-labelled lactotrophs (arrows) were observed after *Men1* gene replacement vector. Scale bars: 100μm; DAPI, nuclear counterstain.

The Society offers their congratulations to Gerard and also to the Young Endocrinologists' Basic Science Prize Lecturer, Carles Gaston-Massuet (London) who won with his lecture entitled 'The Wnt/β-catenin effector Tcf3/TCF7L1 is required for normal hypothalamic-pituitary development'.

SOCIETY FOR ENDOCRINOLOGY
BES 2013

The one word that consistently comes up when talking about the Society over the last 12 months is 'change'... for the good, of course. We have changed how we apply the Society values - ENGAGE, SUPPORT, ADVANCE - as well as the Society's new identity. The Society BES 2013 was the platform for this launch and we hope delegates saw a notable change at this year's conference.

The Society conducted a new series of market research activities with delegates through on-the-spot questions, interactive focus groups and a video diary room. This gave delegates a unique opportunity to feed back their thoughts and experiences on a range of matters relating to the Society, the membership and the future. The results will be published in the next issue of *The Endocrinologist* - thank you to everyone who participated!

We welcome your feedback about the Society BES meeting and Society activities in general.

Visit www.endocrinology.org/new-era

or email endocrinologist@endocrinology.org.

PRIZE WINNERS AT SOCIETY BES 2013

Congratulations to all prize winners at the Society BES. Here is a selection of the top prizes awarded during the meeting:

In the Young Endocrinologists' Prize Session, the top-scoring basic science oral communication was presented by Zaki Hassan-Smith (Birmingham) entitled '11β-HSD1KO mice are protected from glucocorticoid dependent age-associated muscle atrophy'. The top-scoring clinical presentation was given by Rita Upreti (Edinburgh) on 'Inhibition of 5α-reductase type 1 with dutasteride impairs insulin sensitivity'.

The poster presentation prizes were hotly contested, but finally the top scoring basic science poster was deemed to be 'Contribution to bone mass and strength of osteoblast GH actions that are independent of local IGF-I production: Lessons from the SOCS2 knockout mouse' by Ross Dobie (Edinburgh) while the clinical prize was won by Ali Abbari (London) for 'Kisspeptin-54 administration stimulates LH pulsatility in women with hypothalamic amenorrhoea'.

A full list of prize winners is available at http://bit.ly/16fjdy7.

Zaki Hassan-Smith

Rita Upreti

Ross Dobie

Ali Abbari

IN THE NEWS

We're pleased to report that news from the Society BES spread far and wide. Pride of place was a *Daily Mail* article on novel research using glucagon and GLP-1 combination infusions to suppress appetite, carried out by Steve Bloom at Imperial College London. With UK circulation figures of over 1 million, this article alone did much to raise awareness of the role of hormones in appetite and, at the time of writing, the story is still being picked up by the international press.

Further reports included the discovery by Akash Sinha (Newcastle upon Tyne) of a link between vitamin D levels and mitochondria in skeletal muscle, which was popular among the leisure and healthy living press. A study by Alexia-Giovanna Abela (Malta) associating infectious disease burden with type 1 diabetes rates by country featured on a plethora of outlets such as Medical News Today and *The Huffington Post*.

CONGRATULATIONS

We hope you all enjoyed playing the 'Spin the Wheel' game on the Society's stand. The lucky winner of the Kindle Fire was Anupam Brahma (Norfolk).

QUIZ SPECTACULAR

Our highly popular Young Endocrinologists' Quiz Night was again a hit at the Society BES 2013. The entertaining night was eventually won by a team named 'Quizzimodo'! For those of you unable to attend, here's our pick of the questions:

Q1. President George HW Bush and his wife Barbara were both diagnosed with what same endocrine condition?

Q2. English tenor singer Russell Watson underwent surgery for what endocrinopathy in 2006?

Q3. Which US President is it proposed had multiple endocrine neoplasia type 2B?

Q4. According to the British Heart Foundation's report 'Physical activity statistics 2012', which European country has the highest percentage of adults that play sport regularly?

Q5. Name the following Society members:

5A. A Slogans Rhymes

5B. A Dry Diva

5C. Meccas Birch

Q6. According to the NHS what is the recommended maximum amount of salt adults are allowed per day?

ANSWERS ON PAGE 16...

A SCIENTIFIC VIEW OF THE SOCIETY BES

This year the Society BES conference had a diverse mix of sessions, providing something of interest for everyone. For me, the highlight was the Applied Physiology Workshop 'Digital copies: exploiting numerical models of biological systems', which illustrated why mathematical approaches are so widely used in data analysis and why systems biology is a key strategic funding area.

The need for mathematical approaches stems in part from the large amount of information available online and through experimentation, which can only be thoroughly interrogated with computational or mathematical techniques. Tom Freeman presented two network-based computational tools. The first, BioLayout *Express* 3D, clusters data according to a Pearson correlation matrix and has been used to analyse the pig transcriptome.[1] Transcripts were grouped according to their expression profile, with co-expressed functionally related genes identified.

The second computational tool generated complex pathway maps using a notation system that allows the expansion of information contained within the map. The need for a standard graphical notation in biology has already been highlighted,[2] but a universally accepted standard is yet to be agreed upon. Pathway maps allow modelling to assess information flow through the system and are likely to prove useful in data interpretation and hypothesis generation. The maps shown by Professor Freeman related to cellular activity, such as macrophage action.[3] In contrast Patrick Hannaert presented a model of the cardiovascular renin-angiotensin system, integrating regulatory influences from several tissue systems. Data generated using the model exhibited similar physiological and pharmacological behaviour to experimentally derived data and may ultimately aid further understanding of this system.

Maria Rodriguez-Fernandez presented her work on cortisol dynamics in depression and post-traumatic stress disorder.[4] Using nonlinear ordinary differential equations, the kinetic parameters of the model were estimated and fit to experimental data from normal and depressed subjects and subjects with post-traumatic stress disorder. The model predicts transitions from normal to disease states, occurring due to changes in the strength of the negative feedback loop and the stress intensity in the neuroendocrine axis.

Overall this fascinating session highlighted the importance of systems biology in the generation of an integrated view of biological processes from the cellular level up to the organism level.

KAREN FEATHERSTONE
Postdoctoral Research Associate, University of Manchester

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1. Freeman TC *et al.* 2012 *BMC Biology* **10** 90.
2. Le Novere N *et al.* 2009 *Nature Biotechnology* **27**(8) 735-741.
3. Raza S *et al.* 2010 *BMC Systems Biology* **4** 63.
4. Sriram K *et al.* 2012 *PLoS Computational Biology* **8**(2) e1002379.

A DELEGATE'S PERSPECTIVE OF THE SOCIETY BES

It was talk of hypothermia, not the hypothalamus, that greeted many delegates who braved freezing conditions in Harrogate to attend this year's Society BES in March. Snow covered the ground, and there were serious concerns the temporary closure of Leeds airport might scupper the arrival of some highly prestigious international speakers. Would the Society BES 2013 fall foul of the big freeze?

It turns out that we endocrinologists are made of sterner stuff. In fact, we attended in record numbers. The opening symposium, with talks from Robert Evans (London), Elizabeta Nemeth (Los Angeles, USA), and Heinz Zoller (Innsbruck, Austria) immediately thawed attendees. The speakers delved into the poorly understood world of how hormones, particularly the peptide hepcidin, regulate iron homeostasis. It was a thoroughly entertaining session which fired the imagination and boded well for the rest of the conference.

Things really began to warm up with a thoroughly engaging Young Endocrinologists' Prize Session sporting excellent studies conducted by future leaders in our field. A particular highlight was Sarah Howles' (Oxford, UK) presentation establishing that the new disorder, autosomal dominant hypocalcemia type-2, is caused by a gain-of-function mutation in the gene GNA11, a completely novel and exciting finding. Some insightful questioning, especially from Paul Stewart, kept all the budding endocrinologists on their toes.

The following day brought less snow and the first two medal lectures. The Dale Medal was given to Ronald Evans (La Jolla, USA), but presented *in absentia* to Johan Jonkers, and the Hoffenberg International Medal was awarded to Fernard Labrie (Quebec, Canada). Both gave overviews of their significant research contributions throughout inspiring scientific careers. Indeed, Professor Labrie's wide-ranging work highlighted the important concept of how peripheral intracrinology should not be ignored in many endocrine-related conditions.

Then onto the poster sessions and the usual plethora of topics and vibrant conversations. The new exhibition hall layout was well received and attracted a large turnout and much discussion during the 2-hour slot. There was even the introduction of a Big Brother style Diary Room for the more vociferous delegate to vent their views!

Overall, the 2013 Society BES was another resounding success. Congratulations to the new Programme Secretary, Chris McCabe, and his team for organising such a well-oiled and intellectually stimulating conference. Their hard graft was clearly evident and I look forward to next year's meeting in Liverpool ... perhaps with slightly less snow!

PAUL FOSTER
Lecturer in Molecular Endocrinology, University of Birmingham

All abstracts from the 2013 Society BES can be viewed at www.endocrine-abstracts.org

CASE REPORTS: NO LONGER THE POOR RELATION

Case reports are vital to the medical community, so why don't most research journals publish them?

In the 1970s, there was a move from so-called 'anecdotal' publications to place emphasis on planned, experimental research. This was compounded by the publishing industry's preference for publishing research papers as they are cited more often, and so boost impact factors, a tool for ranking journals within their fields.

Endocrinology, Diabetes & Metabolism
CASE REPORTS

So why the recent resurgence in case reports?

Case reports are intrinsically popular in the medical community:

- They play a vital role in medical education, giving deeper understanding and real-life application.
- They facilitate the discovery of new diseases and unexpected effects, and allow for communication of new ideas and techniques.
- They give a more holistic picture of a patient, introducing variables that are overlooked in clinical trials, such as history and psychosocial aspects.
- Junior doctors garner valuable experience in academic writing by using case reports as scholarly stepping stones and tools for professional development.
- They represent the vast majority of patients who have multiple clinical conditions who would be excluded from clinical trials.

So case reports clearly fulfil a role that evidence-based medicine does not. They do this cheaply and quickly. As retrospective narratives, the financial and time costs associated with conducting research are not incurred.

Furthermore, case reports complete the cycle linking basic science and medicine, fulfilling the opposite function of translational research, acting as a clinical catalyst for the birth of new hypotheses and research.

The Society for Endocrinology aims to support and advance all endocrinologists, and is pleased to endorse a new resource to further medical education and clinical practice by publishing and linking together case reports dedicated to the field.

Endocrinology, Diabetes & Metabolism Case Reports will facilitate discovery, connections and comparisons by offering a product that is greater than the sum of its parts, achieved by highly classified content that allows for sophisticated search and discovery.

Endocrinology, Diabetes & Metabolism Case Reports will be led by Dr Maralyn Druce, Reader in Endocrine Medicine and Consultant in Endocrinology, Barts and the London Medical School, and will be online-only and open access, ensuring that publication is rapid and that readers worldwide will have free perpetual access to all content.

Endocrinology, Diabetes & Metabolism Case Reports is now open for submissions. Visit www.edmcasereports.com to submit your case report and find out about the exclusive discount for Society for Endocrinology Members. For queries, email edm@bioscientifica.com.

STREAMLINED CPD

The CPD Committee of the Federation of the Royal Colleges of Physicians (RCP) invited learned professional bodies, including the Society for Endocrinology, to nominate five international events to bypass the usual application process. This will enable UK consultant attendees to claim CPD credits without the provider having to submit an individual application for approval.

The Clinical Committee identified the following meetings (diabetes events were excluded):

- ENDO 2013
- 15th European Congress of Endocrinology
- 13th International Pituitary Congress
- 37th Annual Meeting of the European Thyroid Association
- ASBMR 2013 Annual Meeting

This will happen annually, and the Society will be able to submit five suggestions for the next cycle at the end of 2013. Suggestions from Society Members are welcome and should be sent to members@endocrinology.org.

If you are fortunate enough to attend one of these meetings and wish to apply for CPD credits via the RCP CPD website, login to http://cpd.rcplondon.ac.uk and choose 'endocrinology and diabetes' as your specialty. Click on the relevant conference (found in date order) and claim your approved external clinical CPD credits!

BioDynamics 2013 – RHYTHMS IN BIOLOGICAL SYSTEMS

WHERE BIOLOGY, MEDICINE AND MATHEMATICS MEET

BRISTOL, 11–13 SEPTEMBER 2013

Endocrinologists have long known the importance of hormone pulsatility for the regulation of gonadotrophin secretion. Indeed, pulsatility seems to be a characteristic of almost all hormones, with the exception of those with long half-lives such as thyroxine. It is becoming clear there is a mathematical basis not only to the emergence of hormone pulsatility but also to the decoding of hormone signals at the level of both G-protein coupled receptors and nuclear receptors.

This conference will cover both clinical and experimental research and concentrate on the endocrine/computational interface of circadian and ultradian hormone rhythms, and why these rhythms are so important for good health. It will include workshops where endocrinologists will be able to discuss their research programmes and data with mathematicians already working on endocrine research questions.

The conference is supported by the Society for Endocrinology.
The early-bird registration deadline is 28 June 2013.
For further information visit www.bio-dynamics2013.org.

ANSWERS TO QUIZ ON PAGE 14

Q1.	GRAVES' DISEASE	**Q5A.**	ASHLEY GROSSMAN
Q2.	PITUITARY ADENOMA	**Q5B.**	DAVID RAY
Q3.	ABRAHAM LINCOLN	**Q5C.**	CHRIS MCCABE
Q4.	IRELAND	**Q6.**	6 GRAMS

NIKKI KIEFFER NURSE COMMITTEE CHAIR

It was great to see so many of you at Society BES 2013! The Nurses' Sessions were well received, and I thank all the speakers once again. The new *Competency Framework for Adult Endocrine Nursing* was launched during the conference.

Thanks to Louise for her article below on the European Neuroendocrine Tumor Society Conference, which discusses the diagnosis and management of these tumours. It is good that so many different disciplines were represented – a true example of teamwork. It is also good to hear how we can learn from each other, and I will ask Louise to share what she learnt about vitamin deficiencies and long-term use of somatostatin analogues.

Finally, a date for your diary: the Society's Endocrine Nurse Update takes place on 16–17 September in Stratford upon Avon. Remember that you can obtain funding in the form of a conference grant from the Society (if you are not using it to attend an overseas meeting). See www.endocrinology.org/grants for details and deadlines. Several patient groups also offer grants; please contact the Society for advice. This will be my last year as Chair, and I would love to see you all in Stratford to say a personal thank you for all your support.

To find out more about our Endocrine Nurse Update, visit www.endocrinology.org/meetings/endocrinenurse

DIAGNOSIS AND TREATMENT OF NET DISEASE

WRITTEN BY LOUISE BREEN

I was fortunate enough to attend this year's 10th Annual European Neuroendocrine Tumor Society (ENETS) Conference in Barcelona, Spain, on 6–8 March.

As a first timer, it was a great experience with a full and interesting programme. The presence of participants from oncology, hepatobiliary, gastroenterology, pathology, genetics, surgery, nuclear medicine, radiology and endocrinology indicated the complex multi-disciplinary teams involved in looking after patients with neuroendocrine tumours (NETs).

The first day began with a postgraduate course covering imaging, staging, treatment and management of NET complications. Clinical case presentations were linked to each session. Days 2 and 3 included Meet the Professor sessions, a review of histopathology, and updates on management and outcomes of NETs, including current guidelines.

The Nurses' symposium was very patient focused and covered nutrition, quality of life issues and adherence. It was great to meet nurses from many specialities, and discuss the common issues associated with these patients, use of validated quality of life tools and adverse effects of different treatments. The association of vitamin deficiencies with long term use of somatostatin analogues was new to me, and is an area I will review in our local practice.

I would recommend this meeting to endocrine nurses who work in neuroendocrine disease at an advanced/specialist level. Costs are reduced if you are a member of ENETS. Members of the UK and Ireland Neuroendocrine Tumour Society (UKI NETS) can apply for complimentary ENETS membership.

LOUISE BREEN
Endocrine Specialist Nurse, King's Health Partners, ENETS Centre of Excellence

Society for Endocrinology

NURSE CORE COMPETENCIES

Competency Framework for Adult Endocrine Nursing... developed to enhance the clinical care that adults with an endocrine disorder receive.

A KEY TOOL FOR ENDOCRINE NURSES AND CLINICAL MANAGER RECRUITERS

SUPPORTING ENDOCRINE NURSES

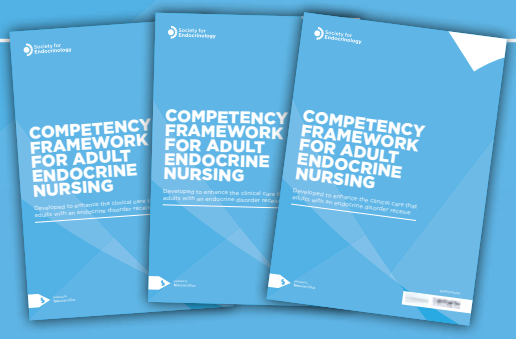
- Identify current level of practice
- Help plan a career path
- Enhance development as professional practitioners

SUPPORTING EMPLOYERS
Clinical Managers and recruiters

- Use this model to ensure consistently high standards of care
- Give a clearer insight into the expertise and competencies of staff
- Assist in organisational planning

SUPPORTING PATIENTS AND THE PUBLIC THROUGH DELIVERING

- Consistently high standards of care
- Increased effectiveness of service provision
- Improved access and choice for care provision



To request your copy of the Competency Framework
call: 01454 642200
email: info@endocrinology.org

For details visit
www.endocrinology.org/endocrinenurse

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We are delighted to highlight the activities of some of our Corporate Supporters here. We thank them for their support and contribution to scientific and clinical endocrinology. Corporate Support is vital to the Society for Endocrinology, enabling us to further our charitable objectives and engage with endocrinologists, supporting their learning and advancing the science of endocrinology.

For further information,

visit www.endocrinology.org/corporate or contact amanda.helm@endocrinology.org

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AN INTERVIEW WITH... HOWARD JACOBS

INTERVIEW BY MILES LEVY

Howard Jacobs seems to me to be a man on top form. He welcomes me into his home, situated in central Primrose Hill, a fashionable area of London with a high concentration of celebrity residents. As I enter, there is a general sense of Bohemian affluence, with smatterings of art and literature on the walls and bookshelves. I get introduced to 'Beanie', Jacobs' 8-year-old granddaughter, who is lying on the sofa reading *Harry Potter;* she has taken the day off school with a bug but seems to be making a dramatic recovery. Jacobs is relaxed in jeans and socks and ushers me into the kitchen. 'I've been very lucky,' he claims with a smile, and we embark on his life story, which tells the origin and modern history of UK reproductive endocrinology.

CURRICULUM VITAE

Howard Jacobs
Born: 9 June 1938, London, UK
Married to Sandra, with three children

Education

1959	BA	Cambridge University
1962	MB BChir	Cambridge University and The Middlesex Hospital Medical School
1965	MRCP	London
1970	MD	Cambridge University
1979	FRCP	London
1992	FRCOG	*Ad eundem*
2006	MA	Queen Mary, University of London (Distinction)

Professional positions

1963	SHO then Registrar, Chase Farm Hospital, Enfield
1965	Leverhulme Research Fellow, Middlesex Hospital Medical School
1967	Registrar, The Middlesex Hospital
1969	Research Fellow (Endocrinology), UCLA
1970	Assistant Professor, Department of Medicine, UCLA Staff Physician (Endocrinology), Harbor General Hospital
1971	Senior Registrar in Medicine, Central Middlesex Hospital / The Middlesex Hospital
1974	Senior Lecturer then Reader in Gynaecological Endocrinology and Chemical Pathology, St Mary's Hospital Medical School Honorary Consultant Physician, St Mary's Hospital
1983	Professor of Reproductive Endocrinology, University College and Middlesex School of Medicine
1985	Civilian Consultant in Endocrinology and Metabolism to the RAF
1998	Emeritus Professor of Reproductive Endocrinology, Royal Free and University College London School of Medicine Honorary Consultant Physician (Emeritus) UCL Hospitals Trust

EARLY LIFE AND CAREER CHOICE

Jacobs is the son of a furniture business owner. He spent most of his childhood in north west London, save a 5-year spell in Philadelphia during the war. At the age of 6 he was given a doctor's bag, and decided then that medicine would be a better career than his original plan of being a train driver. He was educated at Malvern College, Worcestershire and Caius College, Cambridge, and completed his clinical training at The Middlesex in 1962.

His early career did not take off at all, and after doing a few peripheral jobs, found he couldn't get back into The Middlesex. He decided to move to the USA, but there was one consultant at The Middlesex Hospital that Jacobs had mentioned to his wife in a positive light: the endocrinologist, Dr John Nabarro. 'What about working for me?' offered Nabarro to Jacobs, who had followed his wife's suggestion and paid Nabarro a visit. With these words, Jacob's long affiliation with endocrinology and The Middlesex began.

ACADEMIC AND CLINICAL ENVIRONMENT

Nabarro told Jacobs that people were starting to measure hormones, which seemed outlandish because of their tiny concentrations in the blood. Endocrine diagnoses were very clinically based at that time. 'We diagnosed Addison's disease by giving 1 litre of fluid, and if less than 800ml came out in the next hour, that suggested reduced free water clearance and was supportive of cortisol deficiency.' Thereafter, quite complex tests on steroid metabolites in 24-hour collections of urine became available. Radioimmunoassays (RIAs) were brand new, but a number of groups had started to apply the technique to endocrinology. The sense of excitement and discovery was very real, and institutions (and personalities) were to become great rivals.

At The Middlesex, Jacobs had a rich combination of ground-breaking clinical and academic experience. He did autoimmune clinics with Deborah Doniach, one of the pioneers of autoimmunity. 'She and Ivan Roitt had recently shown that mixing serum from patients who had Hashimoto's disease with extracts of thyroid tissue caused precipitins, due to a phenomenon that was unknown at the time.' The scientific environment was 'an incredible milieu' and, whilst a junior research fellow, Jacobs set up The Middlesex's growth hormone assay, guided

Howard Jacobs *CURRICULUM VITAE*

Professional activities

Include:

1982–1983	Person Appointed, Public Enquiry into Depo Provera
1983–1988	Member, MRC Advisory Committee on Oral Contraception
1984–1988	Member, Grants Committee B, MRC Systems Board
1985–1996	Member, Steering Committee, National External Quality Control Scheme
1983–1998	Member, Committee on Safety of Medicines
1989–1998	Member, Subcommittee on Oral Contraceptives, Committee on Safety of Medicines
1990–1998	Member, National Biological Standards Board
1990–1998	Member, Scientific and Advisory Committee, NIBSC
1991–1998	Member, MRC Working Party on Hormone Replacement Therapy
1993–1995	President, RSM Endocrine Section
1993–1996	Chairman, British Fertility Society
1993–1998	Chairman, Biologicals Subcommittee, Committee on Safety of Medicines
1998–2001	President, British Fertility Society
1999–2002	Chairman, Public Relations Committee, Society for Endocrinology
1999–2003	Chairman, MRC Steering Group, Contraceptive Development Network, Centre for Reproductive Biology, Edinburgh

Academic supervision

Students include:

FJ Bramble MS, S Franks MD, J Hutton PhD, M Hull MD, Z van der Spuy PhD, N Abdulwahid PhD, W Hague MD, G Conway MD, E Owen MD, J McDougall MD, A Balen MD, R Agrawal PhD

Publications

More than 250 research papers and three textbooks

by a pretty useful senior research fellow called Peter Sönksen. Having completed his MD in growth hormone, like any self-respecting academic, he went to the University of California, Los Angeles, for his 'BTA' (Been to America).

'The scientific climate of '69-'70 was like going into The Cavern in Liverpool ... coming out saying "those guys are good"!'

EXCURSION TO AMERICA AND THE START OF REPRODUCTIVE ENDOCRINOLOGY

He describes with childlike enthusiasm the 'open skies of the America of the late 1960s. There was a heady mix of brilliant professors of endocrinology, an air of optimism, an abundance of money, and a spirit of collaboration that seemed alien to an English neophyte like Jacobs. Bill Odell, world-famous professor of endocrinology, took Jacobs under his wing, although he thought his UK apprentice a little stiff: 'If you don't stop calling me sir, and refuse to call me Bill, there's no point in you working here son.' Jacobs says of the scientific climate, 'It was like going into The Cavern in Liverpool, watching four blokes play, and coming out saying "those guys are good"!'

Money was flowing, as Nixon had ring-fenced $5 billion for medical research. On a daily basis, new discoveries were being made. Bill Odell would write the latest breakthrough on a blackboard. 'One day we saw "Pyro-Glu-His" on the board' – the structure of thyrotrophin-releasing hormone, which had been discovered in a next door laboratory. This work would shortly win the 1977 Nobel Prize.

Jacobs helped to set up a new assay for gonadotrophins and studied their changes in puberty. Through *in vivo* studies, he showed that puberty was tightly controlled by a supersensitive feedback system. 'What could be more important than reproduction?' asks Jacobs. Influences included Gerald Swyer (of 'Swyer's syndrome') and Jean Ginsberg, pioneering UK reproductive endocrinologist of the day. He attended a speech by the US Secretary of State at the US Endocrine Society, who extolled the virtues of research in reproduction. By this time, his mind was set on a career in reproductive endocrinology.

He studied the control of ovulation in rats, showing that the mid-cycle luteinising hormone (LH) surge was largely under the control of the ovarian hormones. He shared an office with a Haitian scientist called Guy Abraham, who had developed a sensitive RIA for oestradiol. ('Wow, a RIA for a steroid!' exclaims Jacobs.) The assay was so sensitive that the changes at different stages of the menstrual cycle could be measured. 'A young woman with small bottles of yellow fluid' (human ovarian follicular aspirate) arrived from the UK laboratory of Bob Edwards, a subsequent Nobel Prize winner. Jacobs laments how Edwards only received the Nobel Prize after becoming too unwell to appreciate it, the award having been blocked for many years by a prejudiced but powerful anti-IVF (*in vitro* fertilisation) lobby.

RETURN TO THE UK

Jacobs came back to the UK brimming with the 'intellectual ferment and transformative atmosphere' of his American experience. He returned earlier than planned, having had a job lined up for him at The Middlesex to replace the Senior Registrar (SR) who was due to take a consultant post elsewhere. Having arrived back home with his wife and three children, he discovered that the SR was still there!

Unemployed and with family commitments, he sought advice from the Dean of Middlesex. 'My boy, never be loyal to an institution because it will never be loyal to you,' exclaimed the Dean. This advice was a little conflicting, as he then gave Jacobs 6 months' of grant money until the SR post finally became available!

Jacobs brought back his reproductive endocrine skills from the USA to develop home-grown human gonadotrophin assays. Prolactin was of increasing clinical interest, with Michael Thorner making considerable progress in this area at Barts. Jacobs obtained a grant whilst still an SR (it was very unusual to get a grant below consultant position), and was recommended a chap named Steve Franks, who was then looking for a research project as he had passed his MRCP too quickly to be eligible for registrar posts.

CONTINUED ON PAGE 22...

AN INTERVIEW WITH... HOWARD JACOBS

...CONTINUED FROM PAGE 21

Franks and Jacobs studied prolactin levels in around 100 women with secondary amenorrhoea without galactorrhoea. To their astonishment, 20 of them had elevated prolactin levels (until then it was believed that hyperprolactinaemia would only be present if there was galactorrhoea). Bromocriptine restored periods and ovulation in these patients without galactorrhoea, which was very exciting and a real treatment advance for women with infertility. Today, we take it for granted that hyperprolactinaemia is a routine consideration in any presentation of secondary amenorrhoea.

'We studied around 100 women with secondary amenorrhoea without galactorrhoea ... to our astonishment 20 had elevated prolactin levels'

DEVELOPING REPRODUCTIVE ENDOCRINOLOGY AS A CLINICAL SPECIALTY

So, clinical reproductive endocrinology was taking off in a big way. Having done 4 years as a SR, it was time for Jacobs to get a consultant job. He was appointed a Senior Lecturer in the gynaecology department at St Mary's Hospital. To get a job in a gynaecology unit was seen by fellow endocrinologists as tantamount to 'career suicide'. Jacobs, however, could see the opportunities for a card-carrying endocrinologist in a gynaecology unit; the complementary skills would allow for more of a sophisticated combined approach to reproductive endocrinology.

The job was combined with a Senior Lectureship in chemical pathology, which allowed a close collaboration with Professor Vivian James, consultant chemical pathologist. Whilst at St Mary's, Jacobs investigated the role of oestradiol and oestrone in women with menopausal symptoms. He also collaborated with a bright SR called Stafford Lightman, who was investigating the role of opiates in hypothalamic function, a study which was published in the *Lancet*.

After 8 years at St Mary's, Jacobs moved back to The Middlesex following John Nabarro's retirement. This period of Jacob's career was an exciting time for the study of polycystic ovary syndrome (PCOS).

THE IMPORTANCE OF OVARIAN ULTRASOUND

A key person in Jacob's research life was Judy Adams, a former nurse and midwife, who had become a talented ultrasonographer. She had an extraordinary ability to visualise the ovary on ultrasound and defined the morphological characteristics of PCOS with beautiful accuracy. Together with Steve Franks, Judy Adams demonstrated that about 20% of the normal population had polycystic ovaries, but without the clinical constellation of PCOS symptoms. Dr, now Professor, Gerard Conway was the research registrar who was working on the relationships between weight, menstrual irregularity, hyperinsulinaemia and hyperandrogenism. This work led the way to the now accepted view that PCOS is a metabolic condition rather than a morphological one, and Conway continues to be a leader in the field at University College London Medical School.

Jacobs describes with animated enthusiasm how Adams could visualise pre-pubertal ovarian follicles on a scan, which allowed them to study the evolution of PCOS during puberty. Inducing puberty in such girls with a gonadotrophin-releasing hormone (GnRH) pump caused a disproportionate rise in LH, which became an important driver for hyperandrogenism. The lesion in PCOS was therefore shown, not surprisingly perhaps, to be in the ovary and not in the hypothalamus or pituitary. 'The normal ovary functions as a bioassay for the pituitary gland, and the uterus as a bioassay for the ovary', claims Jacobs. The penny starts to drop for me about the right way to think about reproductive endocrinology (and I am starting to find these interviews a wonderful way of learning endocrinology!).

SITTING AT THE TOP TABLE

In the early 1980s, there was concern that hormone replacement therapy might cause endometrial cancer, and Depo Provera was being introduced by the pharmaceutical company Upjohn. Jacobs was investigating progestogens, so was a natural person for the Committee on Safety of Medicines (now the MHRA) to ask for advice. He was eventually asked to sit on the Committee, which he describes as one of the most important aspects of his career, having the ability to influence prescribing habits at a population level. The monthly meetings provided the most intense postgraduate education anyone could ask for. 'There were magnificent people sitting round that table.' These included Mike Rawlins, later Chairman of NICE, and Mike Vessey, one of the most eminent professors of pharmacoepidemiology in the world.

The actual table they sat round was so long that microphones were worn in order to be heard. At his inaugural meeting, there was a prolonged discussion about whether to send a letter to GPs regarding the safety of the contraceptive pill. Jacobs whispered playfully in Vessey's ear, 'It might be better if we sent them a French letter.' With a ripple of laughter from the rest of the group, Jacobs realised he had forgotten to turn his microphone off! He was duly accepted and started a very happy 15 years at the MHRA, including 5 years as the Chairman of one of its subcommittees.

SEMINAL ROLE IN THE DEVELOPMENT OF FERTILITY TREATMENTS

Jacobs pioneered the use of pulsatile GnRH therapy to induce ovulation. He describes how the novel pumps were based on the same concept as the newly developing insulin infusions introduced by the diabetologists. The GnRH pumps led to successful pregnancies in patients with Kallmann syndrome, which was 'mind-bending' at the time and massively exciting. The close tracking of follicles showed that as one became dominant and caused the LH surge, the others regressed. This confirmed his earlier observations in rats that the timing of the LH surge was determined by the ovary and not at the hypothalamic level.

IVF was a developing field, mainly restricted to the private sector. The powers-that-be believed that Jacobs could help advance the field. He was asked to teach the IVF trainees, and agreed, with the proviso that their salaries would be paid for, by the private clinics. An Australian trainee put a commonly accepted IVF conundrum to Jacobs: 'The real problem is every time we stimulate the ovary, the LH surge wrecks all the eggs.' Jacobs decided that a way round this was to block the LH surge by pretreatment with a superactive GnRH analogue, and to administer low dose gonadotrophins to allow multiple follicles to develop simultaneously. It worked and was a very important advance, because the embryological techniques at the time required as many oocytes as possible to be collected.

Jacobs goes on to describe with great pride the clinical reproductive endocrinology unit he set up at The Middlesex. There was a weekly research seminar attended by ultrasonographers, nurses and research fellows from The Middlesex, usually with attendees from other units as

well. All patients on fertility treatment were reviewed at that meeting, and research projects were discussed in a remarkably open and frank way. About seven members of that group continue to meet socially twice a year as the Alternative Ovarian Club. New outpatients had their investigations prior to the clinic appointment, so that relevant results were available at the first appointment, where the key management plans could be made. Although clinically very efficient, this was not making the hospital any money. Two new, inexperienced and very young departmental managers told Jacobs that, despite his protestations, they had resolved to alter this situation; 'Don't you worry Howard, me and Irene will fix it.' It was with those words that Jacobs realised he did not like the direction the NHS was taking and it was time to leave. And he hasn't looked back since.

LIFE AFTER RETIREMENT

Jacobs has an impressive array of interests and talents outside medicine. He fully accepts he has had a wonderfully rich medical career, but is now playing catch-up in other areas of his life. He is refreshingly unmisty-eyed about days gone by in clinical medicine, and is very much living for the present and the future. I like the way he had to dig deep to remember many of his achievements, suggesting he does not ruminate about his successes. He felt moved to send me his CV after the interview in case he left anything important out! He now chairs a medical advisory committee, but has essentially made the break.

'Jacobs has an impressive array of talents outside medicine ... he has had a wonderful career but is now playing catch up.'

He is passionate about books and film. He hosts a regular monthly film club at his home cinema (the Primrose Hill set will have lots of insider knowledge). He shows me the big screen downstairs and demonstrates his sound system which surrounds the room with a Tchaikovsky symphony, and the impish look in his eye is infectious. He is currently reading for a PhD in film studies and his dissertation is on early Disney. Jacobs wants me to tell everyone to watch the film 'Bigger than Life' starring James Mason (apparently a very relevant film for endocrinologists, with a dramatic twist at the end). He also insists that I read *Ill Fares the Land* by Tony Judt, which outlines the origins of today's disordered moral compass.

THE FUTURE

Jacobs is a political animal and clearly veers to the left. We have a long chat about the recent changes in medicine, and he worries about the financial and social landscape for his children and grandchildren. He has strong views about the effects of the Thatcher and Reagan era, and the general loss of societal values. He has three daughters: a social community worker, a painter and a lecturer in psychosocial studies. His wife, who originally worked in community development and teaching and is now a photographer, seems to have been ferrying grandchildren around all day (they have five in total), in between making sure Jacobs has made me lunch and drinks (which he has). She is keen to point out that their beautiful house is not down to a combined NHS and teacher's salary, asking if Jacobs has mentioned Uncle Monty! I never got a chance to find out more about Uncle Monty.

I realise it is far later than I planned, I've missed my intended train and it is time to go. As I sit on the train back home, I reflect on our conversation and Jacobs' career and current life. He played a seminal role in the development of UK reproductive endocrinology, reaching the pinnacle of his field, but throughout seems to have retained a healthy scepticism of the bigger picture, rather than being swallowed up by his own achievements. I think this is a large part of why he is enjoying life post-retirement.

Before I left, I told him that I intend to take a leaf out of his book in terms of my own extra-curricular interests, and he emphasised the importance of having a life outside medicine to prepare for retirement. 'I think it was Shakespeare who said "there is a world elsewhere",' says Jacobs, a quote from Coriolanus as he turned his back on the political storm of the Roman empire. Howard Jacobs is a man who has definitely not turned back since retiring from medicine, and it seems to be suiting him just fine.

MILES LEVY
EDITOR, THE ENDOCRINOLOGIST

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You can read about their work on pages 18-19.

LEGENDS AND FACTS: POPULATION SCREENING FOR AIP MUTATIONS IN NORTHERN IRELAND

WRITTEN BY SERBAN RADIAN & MARIA HERINCS

THE SCIENCE BEHIND THE LEGEND

Ireland's folklore has long been preoccupied with giants. Recent discoveries suggest that its stories, including that of Finn McCool and the Giant's Causeway, and Ulster's numerous landmarks mentioning giants, may actually represent something with real roots in fact.

Giants are within the realms of the endocrinologist because they have a growth hormone secreting pituitary tumour that has developed before puberty. It has always been felt that gigantism has a genetic flavour, although until recently there has been little science to substantiate this myth.

Our group from Barts and the London School of Medicine, Queen Mary University of London led by Márta Korbonits, have collaborated with the Departments of Clinical Genetics and the Regional Endocrinology Centre in Belfast, to put some science behind the legend of the Irish giant.

THE AIP GENE AND ITS IRISH ROOTS

The discovery of a predisposition to young-onset acromegaly and gigantism in several Northern Irish families and their connection with the famous Irish giant Charles Byrne has been shown by Márta's group to be due to a founder mutation in the AIP gene.[1] Many current and historical patients with gigantism have been traced back to a small region at the border of South Derry and East Tyrone, and all studied DNA samples share precisely the same AIP mutation. This, in combination with the fact that the penetrance of the gene is low (10-30%), lends support to the hypothesis that this mutation may be relatively frequent in this geographical area, and may be the explanation for the many legends of Irish Giants.

Dr Barry collects a sample

IRISH HOSPITALITY, MEDIA COVERAGE AND COLLECTING SAMPLES

Realising that this part of the world is very special in terms of the genetics of pituitary tumours, we decided to go on a genetic epidemiology 'expedition' to two small Northern Irish towns over two weekends in February and March 2013. We travelled with the following research questions in our minds: how prevalent is this rare gene variant in the population of this small area? To what extent might this affect the local population? Do they need to be screened more widely?

To answer our questions, we needed to find a way of persuading the local population to give us samples of saliva for genetic testing! A local man, Brendan Holland, himself a former patient, and his family and friends, were enthusiastic supporters of the expedition and a great help in providing local knowledge and support. It was Brendan's idea for us to set up a 'recruiting stand' in local Tesco stores. A TV documentary, a number of radio interviews, local advertising and the frequented location led to a large number of people presenting for screening. Will the weekend shop ever be the same again?

Giving up 10 minutes of time and providing personal details, as well as 2ml of saliva for DNA extraction, may not seem like much, but it is probably not what most of us have in mind when we rush out for our shopping at the local supermarket!

With the ideal mixture of determination, resourcefulness and skill from all those involved, but most of all, with the generosity of the volunteers taking part in the study, the team managed to collect an impressive 956 saliva samples in 48 hours (collecting samples over 12 hours each day at about 19 samples per hour).

COMMUNICATION ISSUES

Hard work and good humour went hand in hand, especially when the great mix of international researchers were coping with the local regional accents and speech nuances. Vice versa, local people had to understand our 'international' English! On one occasion, while our excellent Italian colleague was explaining how to provide a saliva sample,

FIND OUT MORE...

READ...

1. Chahal HS *et al*. 2011 *New England Journal of Medicine* **364** 43–50.

VISIT...

www.fipapatients.org, a website to increase awareness about Familial Isolated Pituitary Adenoma (FIPA).

WATCH...

BBC news report on this research: http://bbc.in/Z3dVkP.

VIEW...

a recording from a Society funded public event: 'A tall story: unravelling the genetics behind Charles Byrne': http://bit.ly/16dZm20.

he asked the volunteer to 'speet' into the test-tube he received the candid reply, "What do you want me to say to it?"

A LIFELONG FRIENDSHIP

We ourselves were enriched by the people we have met and have grown to love and admire them in such a short time: our new friends Brendan and all his family members, our colleagues from Belfast (Lisa Bradley, Michal Azensztejn, Patrick Morison, Brew Atkinson and Steve Hunter) as well as Ronan McClosky and many other helpers. Special thanks go to the extremely generous and kind study participants for patiently putting up with our inquisitive questions and trusting us with their personal information and DNA.

What we hope to achieve with this research, in addition to our scientific goals, is to serve the local community and increase awareness for AIP-related disease, extremely rare in the world at large but not so rare in this area. Immediate signs of success were evident: volunteers came intentionally to our cabins, after learning about the study in the local media. Some brought photographs, newspaper cuttings and stories of local 'giants', many of which are not known to the medical community. We were also visited by parents of (very) tall children, and were able to point them in the right direction, possibly leading to early discovery and treatment, something which our previous studies have already achieved in our known AIP families and which will be an important outcome of our community screening initiative.

SERBAN RADIAN MD, PHD, MARIE CURIE FELLOW, AND MARIA HERINCS MD, PHD STUDENT

Members of Márta Korbonits' laboratory are supported by the Wellcome Trust, William Harvey Research Foundation, an unrestricted education grant from Pfizer, an EU Marie Curie Fellowship, NIHR and Barts and the London Charitable Trust.

Colleagues and volunteers who helped in the sample collection, including authors of this article: back row 3rd and 4th from the left.

A local lady brought a newspaper cutting from May 1913 showing her 21-year-old uncle arriving to Canada from Ireland. The uncle, no doubt suffering from gigantism, unfortunately died within a month of having this picture taken, possibly of a hypertensive crisis.

ARE YOU SITTING COMFORTABLY?

WRITTEN BY EMMA WILMOT

How many hours do you spend sitting during the average day? It's a tricky question to answer accurately, but, if you estimate that more than half of your waking hours are spent sitting, then you simply must read on.

As part of my PhD, I recently conducted a meta-analysis to quantify the impact of excess sitting on some key health outcomes.[1] The publication of this study resulted in a flurry of national and international media attention.

'Going to the gym for 30 minutes in the evening is simply not enough to reverse the adverse metabolic consequences of prolonged sedentary behaviour'

In summary, 18 studies with almost 800,000 participants from across the globe were included. Ultimately, excess sitting doubled the risk of diabetes, cardiovascular disease and cardiovascular mortality. While you might feel that the conclusions reached are intuitive, you may be more surprised by the finding that the association of excess sitting with diabetes and cardiovascular mortality persisted when adjusted for physical activity. In other words, if you sit all day, going to the gym for 30 minutes in the evening is simply not enough to reverse the adverse metabolic consequences of prolonged sedentary behaviour.

The findings of this meta-analysis have far-reaching implications. The opportunities for sedentary behaviours are ubiquitous (e.g. travelling by car, sitting at a desk, sitting to read or use the computer, sitting watching television) with the average adult spending approximately 50–60% of their day sitting.[2] Many of us try to reassure ourselves that we are leading a healthy lifestyle by attempting (and often failing) to meet the recommend 30 minutes of moderate-to-vigorous physical activity on most days of the week. However, as I have demonstrated, this simply may not be enough.

Recent studies have identified that substituting sitting for light physical activity (very slow walking for instance) can have a significant impact on glucose metabolism. Breaking up periods of prolonged sitting with 2-minute bouts of light intensity activity every 20 minutes has been shown to result in a 24% reduction in post-prandial glucose area under the curve and a 23% reduction in insulin area under the curve, compared with uninterrupted sitting.[3]

'Simply standing and moving around more will reduce post-prandial glucose and potentially protect from diabetes'

Interestingly, the reductions in glucose and insulin in this study were similar for both light activity and moderate physical activity conditions, demonstrating that small changes in activity levels are adequate for improvements in glucose and insulin. This is an important message to communicate to our patients, many of whom are unable to exercise due to back ache, joint pains etc. Simply standing and moving around more will reduce their post-prandial glucose and potentially protect them from developing diabetes.

Lipoprotein lipase is a key protein in the pathway from muscular inactivity to poor health outcomes. Immobility in rats leads to a significant reduction in postural muscle lipoprotein lipase activity, a change which is associated with blunted triglyceride uptake, reduced plasma high density lipoprotein levels and cardiovascular disease.[4,5]

Studies of skeletal gene expression in humans have also identified that sedentary activity, compared with light physical activity, is associated with changes in the expression of genes which regulate inflammation, and lipid and carbohydrate metabolism, leading to the proposal that sedentary time may result in reduced fatty acid transport in skeletal muscle, an accumulation of intracellular fatty acids and less GLUT4 glucose transporter translocation, resulting in reduced insulin-induced glucose uptake.[6,7]

In summary, excess sitting has a rapid deleterious impact on insulin resistance and glycaemia which is reversible by simply standing and moving around. The time has come to think beyond the daily 30 minutes of exercise which we all strive for, and to start to think more carefully about what we do with the remaining 23.5 hours of the day.

EMMA WILMOT
Clinical Research Fellow, Diabetes Research Unit, University Hospitals of Leicester

IN THE NEWS...

This study obtained widespread media coverage including BBC News Online, *Daily Mail*, *Daily Express* and the *Evening Standard*.

To read more, visit http://bbc.in/16raVVB.

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5. Hamilton MT *et al.* 2008 *Current Cardiovascular Risk Reports* **2** 292.
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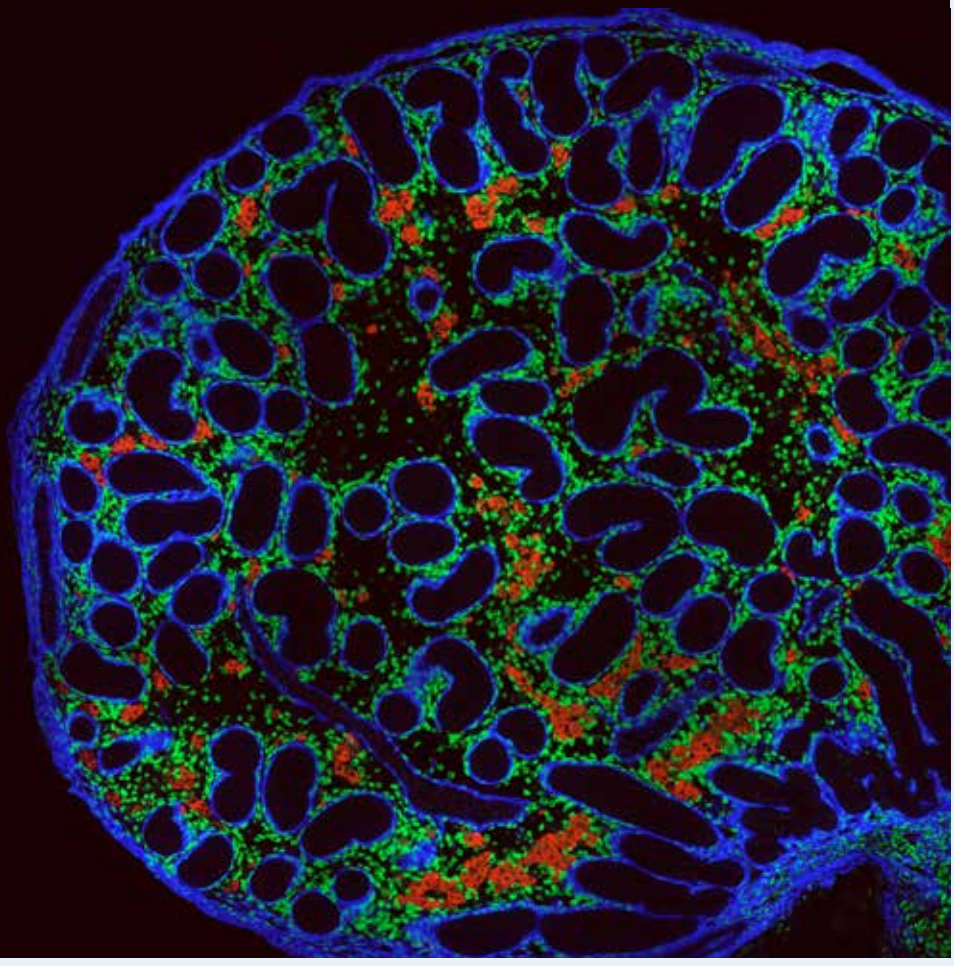
IMAGES IN ENDOCRINOLOGY

Welcome to this new section of *The Endocrinologist*. Each edition, we will bring you highlights from our Cover Art Competition, showcasing the best images in endocrinology.

COVER IMAGE FROM *JOURNAL OF ENDOCRINOLOGY*, FEBRUARY 2013

Pivotal endocrine event in making a male: testosterone production by fetal Leydig cells. The image shows an embryonic day 21.5 rat fetal testis immunostained for 3β-hydroxysteroid dehydrogenase (red) to mark the steroidogenic fetal Leydig cells. Smooth muscle actin (blue) indicates the boundaries of the seminiferous cords and blood vessels and COUP transcription factor II (green) highlights undifferentiated mesenchymal cells. Tiled confocal laser scanning microscopy image compiled of 40× tiles.



Credit: **S van den Driesche & R Sharpe,** MRC/UoE Centre for Reproductive Health, Queen's Medical Research Institute, Edinburgh, UK.

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